



CASE LD0283 DIV 1

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April 9, 2004
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

BENIGNI ET AL.

APPLICATION NO: 10/805,724

FILED: MARCH 22, 2004

FOR: METHODS FOR THE PREPARATION, ISOLATION AND
PURIFICATION OF EPOTHILONE B AND X-RAY CRYSTAL
STRUCTURES OF EPOTHILONE B

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INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed within three months of the filing date of the application. Therefore, no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-3880.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

The listed references are of record in parent Application No. 10/668,032 filed September 22, 2003, and copies are available therein. However, applicants are willing to send copies of any or all of these references at the Examiner's request.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

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FORM PTO-1449
INFORMATION DISCLOSURE STATEMENT

Docket No.: LD0283 DIV1 Sheet 1 of 6
 Serial No.: 10/805,724 Group:
 Applicant: Benigni et al.
 Filing Date: March 22, 2004

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	08/856,533	5/14/97	Nicolaou, K., et al.			5/14/97
	AB	08/923,869	9/4/97	Nicolaou, K., et al.			9/4/97
	AC	60/032,864	12/13/96	Nicolaou, K., et al.			12/13/96
	AD	6,194,181 B1	2/27/01	Hofmann, H., et al.			2/12/99
	AE	6,204,388 B1	3/20/01	Danishefsky, S.J., et al.			2/24/99
	AF	6,211,412 B1	4/3/01	Georg et al.			3/29/99
	AG	6,242,469B1	6/5/01	Danishefsky et al.			12/3/97
	AH	6,316,630B1	11/13/01	Danishefsky et al.			6/6/00
	AI	6,369,234B1	4/9/02	Danishefsky et al.			10/11/00
	AJ	6,380,227B1	9/7/00	Mutz			4/30/02
	AK	6,613,912	9/2/03	Hoefle et al.			4/16/01

FOREIGN PATENT DOCUMENTS

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	BA	4138042.8	5/27/93	Germany (German and English abstract)			
	BB	19639456.2	5/29/97	Germany (German and English translation)			
	BC	19542986.9	5/29/97	Germany (German and English translation)			
	BD	19636343.8	3/5/98	Germany (German and English abstract)			
	BE	19645361.5	4/30/98	Germany (German and English abstract)			
	BF	19645362.3	4/30/98	Germany (German and English abstract)			
	BG	19647580.5	5/28/98	Germany (German and English translation)			
	BH	19701758	7/23/98	Germany (German and English abstract)			
	BI	19707505.3	9/3/98	Germany (German and English abstract)			
	BJ	19713970	10/8/98	Germany (German and English abstract)			
	BK	19720312	11/19/98	Germany (German and English abstract)			
	BL	19821954	11/19/98	Germany (German and English abstract)			
	BM	879 605	11/25/98	Europe (German and English abstract)			
	BN	19726627	12/24/98	Germany (German and English abstract)			
	BO	93/10121	5/27/93	World (PCT as published and English abstract)			
	BP	97/19086	5/29/97	World (PCT as published and English translation)			
	BQ	98/08849	3/5/98	World (PCT as published and English abstract)			
	BR	98/22461	5/28/98	World (PCT as published and English translation)			
	BS	98/24427	6/11/98	World			

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Docket No.: LD0283 DIV1 Sheet 2 of 6
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 Applicant: Benigni et al.
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	BT	98/25929	6/18/98	World (PCT as published and priority documents: U.S. 60/032,864, 08/856,533, 08/923,869)			
	BU	98/38192	9/3/98	World (PCT as published and English abstract)			
	BV	98/47891	10/29/98	World (PCT as published and English abstract)			
	BW	99/01124	1/14/99	World			
	BX	99/03848	1/28/99	World (PCT as published and English abstract)			
	BY	99/07692	2/18/99	World (PCT as published and English translation)			
	BZ	99/39694	8/12/99	World (PCT as published)			
	BAA	99/42602	8/26/99	World (PCT as published)			
	BAB	99/43320	9/2/99	World (PCT as published)			
	BAC	00/37473	6/29/00	World (PCT as published)			
	BAD	00/00485	1/6/00	World (PCT as published and English translation)			
	BAE	00/66589	11/9/00	World (PCT as published)			
	BAF	99/43653	9/2/99	World (PCT as published)			
	BAG	99/02514	1/21/99	World (PCT as published)			
	BAH	00/31247	6/2/00	World (PCT as published)			
	BAI	00/49021	8/24/00	World (PCT as published)			
	BAJ	99/67252	12/20/99	World (PCT as published)			
	BAK	99/27890	6/10/99	World (PCT as published)			
	BAL	99/54319	10/28/99	World (PCT as published)			

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	CA	Balog, A., et al., "Total Synthesis of (-)-Epothilone A", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 23/24, 2801-2803 (1996)
	CB	Bertini, F., et al., "Alkenes from Epoxides by Reductive Elimination with Magnesium Bromide-Magnesium Amalgam", <i>Chem. Commun.</i> , 144 (1970)
	CC	Bollag, D.M., et al., "Epothilones, A New Class of Microtubule-stabilizing Agents with a Taxol-like Mechanism of Action", <i>Cancer Res.</i> 55, No. 11, 2325-2333 (1995)
	CD	Fujisawa, T., et al., "Deoxygenation of Epoxides to Olefins with FeCl ₃ - n-BuLi System", <i>Chem. Lett.</i> , 883-886 (1974)

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)

CE	Fujiwara, Y., et al., "Reductive Coupling of Carbonyl Compounds to Olefins by Tungsten Hexachloride-Lithium Aluminum Hydride and Some Tungsten and Molybdenum Carbonyls", <i>J. Org. Chem.</i> , Vol. 43, No. 12, 2477-2479 (1978)
CF	Gladysz, J. A., et al., "Deoxygenation of Epoxides by Metal Atom Cocondensation", <i>J. Org. Chem.</i> , Vol. 41, No. 22, 3647-3648 (1976)
CG	Hofle, G., et al., "Epothilone A and B – Novel 16-Membered Macrolides with Cytotoxic Activity: Isolation, Crystal Structure, and Conformation in Solution", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 13/14, 1567-1569 (1996)
CH	Hofle, G., et al., "N-Oxidation of Epothilone A-C and O-Acyl Rearrangement to C-19 and C-21 –Substituted Epothilones", <i>Angew. Chem. Int. Ed.</i> , Vol. 38, No. 13/14, 1971-1974 (1999)
CI	Inokuchi, T., et al., "Opening of Epoxides to Olefins or Halohydrins with Vanadium(II)-Tetrahydrofuran or Vanadium(III)-Tetrahydrofuran Complexes", <i>Synlett</i> , No. 6, 510-512 (1992)
CJ	Kowalski, R. J., et al., "Activities of the Microtubule-stabilizing Agents Epothilones A and B with Purified Tubulin and in Cells Resistant to Paclitaxel (Taxol®)" <i>J. Biol. Chem.</i> , Vol. 272, No. 4, 2534-2541 (1997)
CK	Kupchan, S. M., et al., "Reductive Elimination of Epoxides to Olefins with Zinc-Copper Couple", <i>J. Org. Chem.</i> , Vol. 36, No. 9, 1187-1190 (1971)
CL	Martin, M. G., et al., "Epoxides as Alkene Protecting Groups. A Mild and Efficient Deoxygenation", <i>Tetrahedron Letters</i> , Vol. 25, No. 3, 251-254 (1984)
CM	McMurry, J. E., et al., "Reduction of Epoxides to Olefins with Low Valent Titanium", <i>J. Org. Chem.</i> , Vol. 40, No. 17, 2555-2556 (1975)
CN	McMurry, J. E., et al., "Some Deoxygenation Reactions with Low-Valent Titanium (TiCl ₃ /LiAlH ₄)", <i>J. Org. Chem.</i> , Vol. 43, No. 17, 3249-3254 (1978)
CO	Meng, D., et al., "Remote Effects in Macrolide Formation Through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 11, 2733-2734 (1997)
CP	Nicolaou, K. C., et al., "An Approach to Epothilones Based on Olefin Metathesis", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 20, 2399-2401 (1996)
CQ	Nicolaou, K. C., et al., "Total Synthesis of Epothilone A: The Macrolactonization Approach", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 5, 525-527 (1997)
CR	Nicolaou, K. C., et al., "Designed Epothilones: Combinatorial Synthesis, Tubulin Assembly Properties, and Cytotoxic Action against Taxol-Resistant Tumor Cells", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 19, 2097-2103 (1997)
CS	Nicolaou, K. C., et al., "The Olefin Metathesis Approach to Epothilone A and Its Analogues", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 34, 7960-7973 (1997)
CT	Nicolaou, K. C., et al., "Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 34, 7974-7991 (1997)

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)

CU	Nicolaou, K. C., et al., "Synthesis of Epothilones A and B in Solid and Solution Phase", <i>Nature</i> , Vol. 387, 268-272 (1997)
CV	Nicolaou, K. C., et al., "Synthesis of Epothilones A and B in Solid and Solution Phase" (Correction to <i>Nature</i> 387, 268-272 (1997)), <i>Nature</i> , 390, 100 (1997)
CW	Raucher, S., et al., "Total Synthesis of (+)-Dihydrocostunolide via Tandem Cope-Claisen Rearrangement", <i>J. Org. Chem.</i> , Vol. 51, No. 26, 5503-5505 (1986)
CX	Sato, M, et al., "Reduction of Organic Compounds with Low-Valent Niobium (NbCl ₅ /NaAlH ₄)", <i>Chem. Letters</i> , 157-160 (1982)
CY	Schinzler, D., et al., "Total Synthesis of (-)-Epothilone A", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 5, 523-524 (1997)
CZ	Schobert, R., et al., "Reduction and Isomerization of Oxiranes and α -Diazoketones by Various Early Transition Metallocenes", <i>Synlett</i> , Vol. 8, 465-466 (1990)
CAA	Sharpless, K. B., et al., "Lower Valent Tungsten Halides. A New Class of Reagents for Deoxygenation of Organic Molecules", <i>J. Amer. Chem. Soc.</i> , Vol. 94, No.18, 6538-6540 (1972)
CAB	Su, D.-S., et al., "Total Synthesis of (-)-Epothilone B: An Extension of the Suzuki Coupling Method and Insights into Structure-Activity Relationships of the Epothilones", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 7, 757-759 (1997)
CAC	Su, D.-S., et al., "Structure-Activity Relationships of the Epothilones and the First In Vivo Comparison with Paclitaxel", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 19, 2093-2096 (1997)
CAD	Victory, S. F., et al., "Relative Stereochemistry and Solution Conformation of the Novel Paclitaxel-Like Antimitotic Agent Epothilone A", <i>Bioorg. Med. Chem. Letts.</i> , Vol. 6., No. 7, 893-898 (1996)
CAE	Winkler, J. D., et al., "A Model For The Taxol (Paclitaxel)/Epothilone Pharmacophore", <i>Bioorg. Med. Chem. Letts.</i> , Vol. 6, No. 24, 2963-2966 (1996)
CAF	Yang, Z., et al., "Total Synthesis of Epothilone A: The Olefin Metathesis Approach", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 1 / 2, 166-168 (1997)
CAG	Bollag, D., et al., "Epothilone, A New Structural Class of Microtubule Stabilizer", Abstract, <i>Proc. Am. Assoc. Cancer Res.</i> , Vol. 36, 86 Meet. 454 (1995)
CAH	Bollag, D., "Epothilones: Novel Microtubule-Stabilising Agents", <i>Expert Opin. Invest. Drugs</i> , Vol. 6, No. 7, 867-873 (1997)
CAI	Bertinato, P., et al., "Studies Toward a Synthesis of Epothilone A: Stereocontrolled Assembly of the Acyl Region and Models for Macrocyclization", <i>J. Org. Chem.</i> , Vol. 61, No. 23, 8000-8001 (1996)
CAJ	<i>Chemical & Engineering News</i> , "Epothilone Epiphany: Total Syntheses", Vol. 74, No. 52, 24-26 (1996)
CAK	<i>Chemical & Engineering News</i> , "First Total Synthesis of Epothilone B", Vol. 75, No. 13, 23 (1997)

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Docket No.: LD0283 DIV1 Sheet 5 of 6
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)

	CAL	<i>Chemical & Engineering News</i> , "Solid-Phase Epothilone Synthesis Used to Create Analog Library", Vol. 75, No. 20, 33 (1997)
	CAM	Claus, E., et al., "Synthesis of the C1-C9 Segment of Epothilons", <i>Tetrahedron Lett.</i> , Vol. 38, No. 8, 1359-1362 (1997)
	CAN	De Brabander, J., et al., "Towards a Synthesis of Epothilone A: Rapid Assembly of the C1-C6 and C7-C12 Fragments", <i>Synlett</i> , Vol. 7, 824-826 (1997)
	CAO	Gabriel, T. and Wessjohann, L., "The Chromium-Reformatsky Reaction: Asymmetric Synthesis of the Aldol Fragment of the Cytotoxic Epothilons from 3-(2-Bromoacyl)-2-Oxazolidinones", <i>Tetrahedron Lett.</i> , Vol. 38, No. 8, 1363-1366 (1997)
	CAP	Gerth, K., et al., "Epothilons A and B: Antifungal and Cytotoxic Compounds from <i>Sorangium cellulosum</i> (Myxobacteria) Production, Physico-chemical and Biological Properties", <i>J. Antibiotics</i> , Vol. 49, No. 6, 560-563 (1996)
	CAQ	Marshall, A., "Total Synthesis of Epothilone", <i>Nature Biotechnology</i> , Vol. 15, No. 3, 205 (1997)
	CAR	Meng, D., et al., "Studies Toward a Synthesis of Epothilone A: Use of Hydropyran Templates for the Management of Acyclic Stereochemical Relationships", <i>J. Org. Chem.</i> , Vol. 61, No. 23, 7998-7999 (1996)
	CAS	Meng, D., et al., "Total Syntheses of Epothilones A and B", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 42, 10073-10092 (1997)
	CAT	Mensing, S. and Kalesse, M., "Generation of Thiazoles by Column Dehydrogenation of Thiazolidines with MnO ₂ ", <i>J. Prakt. Chem.</i> , Vol. 339, No. 1, 96-97 (1997)
	CAU	Mulzer, J. and Mantoulidis, A., "Synthesis of the C(1)-C(9) Segment of the Cytotoxic Macrolides Epothilone A and B", <i>Tetrahedron Lett.</i> , Vol. 37, No. 51, 9179-9182 (1996)
	CAV	Nicolaou, K., et al., "Chemistry, Biology and Medicine of Selected Tubulin Polymerizing Agents", <i>Pure Appl. Chem.</i> , Vol. 71, No. 6, 989-997 (1999)
	CAW	Nicolaou, K., et al., "Total Synthesis of Epothilone E and Related Side-chain Modified Analogues Via a Stille Coupling Based Strategy", <i>Bioorg. Med. Chem.</i> , Vol. 7, No. 5, 665-697 (1999)
	CAX	Schinzer, D., et al., "Studies Towards the Total Synthesis of Epothilones: Asymmetric Synthesis of the Key Fragments", <i>Chem. Eur. J.</i> , Vol. 2, No. 22, 1477-1482 (1996)
	CAY	Taylor, R. and Haley, J., "Towards the Synthesis of Epothilone A: Enantioselective Preparation of the Thiazole Sidechain and Macrocyclic Ring Closure", <i>Tetrahedron Lett.</i> , Vol. 38, No. 12, 2061-2064 (1997)
	CAZ	Schinzer, D., et al., "Syntheses of (-)-Epothilone A", <i>Chem. Eur. J.</i> , Vol. 5, No. 9, 2483-2491 (1999)
	CBA	Schinzer, D., et al., "Syntheses of (-)-Epothilone B", <i>Chem. Eur. J.</i> , Vol. 5, No. 9, 2492-2500 (1999)

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)

	CBB	Nicolaou, K. C., et al., "Synthesis and Biological Properties of C12,13-Cyclopropylepothilone A and Related Epothilones", <i>Chemistry & Biology</i> , Vol. 5, No. 7, 365-372 (1998)
	CBC	Altmann, K.H., et al., "Epothilones and Related Structures – A New Class of Microtubule Inhibitors With Patent In Vivo Antitumor Activity," <i>Biochim. Biophys Acta</i> , 1470 (2000)
	CBD	Nicolaou et al., "Total Synthesis of Epothilone E and Analogs with Modified Side Chains Through The Stille Coupling Reaction", <i>Angew. Chem. Int. Ed.</i> 37, 84-87 (1998)
	CBE	Nicolaou et al., "Total Synthesis of Oxazole- and Cyclopropane-Containing Epothilone B Analogues by the Macrolactonization Approach", <i>Chemistry, European Journal</i> , Vol. 3, No. 12, 1971-1986 (1997)
	CBF	Nicolaou et al., "Chemical Biology of Epothilones", <i>Angew. Chem. Int. Ed.</i> , 37, 2014-2045 (1988)

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